Telomere Territory and Cancer

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Editor

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This book is dedicated to:
All the cancer patients who allowed us to learn so much from them, they surely earned an artistic, sincere, moral support, and compassionate medical care.

Preface

Telomeres define and predict the fate of our cells, and are capable to direct the manner of quality and the quantitative values in the specific biological and molecular events. Telomeres could be also named as 'Frontiers in cells'

By looking at a carved tree, we realize the multifarious position of circles indicative of its age. But, in human, it is rather more complicated and we are exposed to the multi-influential factors, cooperating with the telomere territory. Therefore, the phenotype, as a sole, could not reflect the real age of the apparently normal and healthy individuals. Such machinery is even more confusing in cancer patients.

Telomeres act as a 'Bio-Polar System' within the cells which could direct and govern further events in our body.

In programming, 'telomeres begin and terminate the cellular life'. Telomeres make the history of cellular fate, health status, the manner, and future of all cell types which contain chromosomal territory. Telomeres act as guard, protect the cells and guarantee the flow of existence and quality of life.

Telomeres, manage and interact with many events for cancer-puzzling. Normal telomere, 'announcer of life'. Abnormal telomeres, 'trigger and predictor of age and cancer'. In tact telomeres, 'end points of natural and health status'. Telomeres are tracer as predictor, and prognostic values in health and malignant conditions. Shorter telomeres direct aberrant function of telomerase and could act as two edged sward.

Remembering the pioneers who discovered the original facts in telomere and telomerase, seems to be essential; Alexei Olovnikov and Leonard Hayflick (early 1970s) by paving the way, later on Elizabeth Blackburn, Carol Greider, and Jack Szostak (1975–1978) the winner of 2009 Nobel Prize, had discovered the key role of telomeres and the enzyme telomerase for the protection of chromosomes. The original work of Russian theorist Alexei Olovnikov during 1970–1973, is highly appreciated. As he defined the root of Greek words for telomeres (telos "end" and meros "part"), it had been clarified that why the end parts of chromosomes are so critical for the cellular fate and life.

Telomeres are not isolated; they are cooperative and interact with the whole machinery of Cell Biology, Genetics, and environment. They affect other cellular and molecular behavior, and could be affected by many targets in the cellular territories.

Moreover, stem cell is reflective of heterogeneity, and cancer stem cell is sign of evolution and valuable contributor to the cancer research. This paradigm together with telomere territory would pave the way in cancer research towards an innovative therapeutic strategy in future.

Focusing on the current book, it was aimed to provide an educational and research package, preferentially based on the data achieved from our original research projects. The paradigms of *in vivo* and *in vitro* assays, as the essential facts, were also included and highlighted within different chapters. By believing in cancer patients' right and trusting the role of genetics and cell biology, this book is developed through a clinical focal point, i.e., telomerase, as a therapeutic and bio-marker in two chapters. Gradually, the structure of chapters focused on introducing an applicable and new strategy in detection of telomerase activity. Further, telomere was explored, and followed by presenting the interaction between telomere, methylation and nutrition.

Impact of cancer stem cell in different malignancies with special focus on breast cancer was also discussed. Finally, in closing highlights, the whole chapters of this book were thoroughly reviewed.

This book reflects a broad insight in which different domains of life, including eukaryotes, prokaryotes, at *in vivo*, *in vitro*, and human levels, and cooperatively within the chapters were discussed. It also shows that how variety of species including model organisms, fungi including yeast, plants, animals, and human could interact with each other in the nature and share a common biological target, i.e., telomere. This is indicative of, (1) A global diversity and selection, and (2) They need to combat against hazards in our environment, producing by them, by relying on the cellular and molecular events and, (3) Struggling to survive, but in a healthy condition. This is a message to 'take care about our environment'.

That was also my honor to invite, as much as possible, a group including the national and international contributors from different centers as well. I was keenly interested in designing the subject of chapters by considering a complementary strategy of relevant issues in the telomere territory. Upon the manner of developmental based the core concepts in provided chapters focus on:

Chapter 1, "Telomerase From aging to human cancers" provides a complementary basis to serve the scientific investigators with the recent advances of telomerase in human cancers and aging.

Chapter 2, "Telomerase: Basic and clinical approaches" provides the key aspects in telomerase. Specifically, discuss our data on, (1) Association between telomerase activity and hTR in primary breast cancer patients, and (2) By considering clinicopathological parameters, expression of hTR and hTERT in the same patients were also included in this chapter.

Chapter 3, "Detection of telomerase activity: A New Strategy for Detecting Low Activity of Telomerase" presents a progressive and essentials techniques for detecting the telomerase activity including the "Trap assay family". In addition, to bypass limitation such as low activity of telomerase, a new strategy has been also provided in which our data is presented.

Chapter 4, "Telomere, Regulation and Tumorigenesis" mainly, focus on the classic information on structure, interaction between telomeres and DNA damage response, gene expression; and regulation of telomeric chromatin. Mechanism of telomere maintenance and Telomere position effect is also provided. Finally, our data on "telomere and telomerase in brain tumors" is included in this chapter.

Chapter 5, "Novel hypothesis on telomere length: heterogenic targets as genomics/ somatic diverse value in breast cancer and brain tumor" explores the genomic-somatic scenario of telomere length which was initially begun in a group of our patients affected with primary breast cancer, by including the follow up study. In second step, the same model of study was conducted in the patients affected with primary brain tumors.

Chapter 6, "Telomere, Methylation and Nutrition" provides the most important facts regarding the impact of nutritional elements on telomere length, DNA methylation and cancer predisposition. By improving the routine diet composition, the process of aging and cancer could be somehow protected. Such plan would provide a positive impact on the longevity and health of next generations in our pedigrees. The final message would be 'balancing the dietary elements'.

Chapter 7, "Cancer stem cell" provides basic Information on stem cells and cancer stem cells. Paradigm of gene- gene interactions and cooperation between telomeres and CD44+/Cd24- marker are discussed. The final word emphasized on the translational impact of this marker '*CSC is the key target for personalized breast cancer management.*'

Mini chapter 8, "Closing highlights: Final statements at a glance" defines telomere territory as a globalizing domain in genetics and cell biology, interacting with many molecular and cellular targets, which dictate our style of life. The new insight include personalized selection, and cancer family indices through which an appropriate approaches could be planned within specific pedigrees as cancer-prone families. This avenue would facilitate to consider the personalized cancer management.

Finally, whatever we learn about cellular duties in our body, there are still many unmasked facts in telomere territory.

I would also like to gratitude the continuous cooperation of surgeons, nurses, the clinical supportive team, and patients in our projects, whose mutual endeavor is sincerely appreciated.

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Contents

Abbreviations and Acronyms

AA	Aplastic anemia
Abl1	V-abl Abelson murine leukemia viral oncogene homolog 1
ACD	Adrenocortical dysplasia
AIDS	Acquired immune deficiency syndrome
AL	Acute Leukemia
ALDH1	Aldehyde Dehydrogenase 1
ALN	Auxiliary Lymph node
ALT	Alternative lengthening of telomeres
AML	Acute myeloid lymphoma
AML	Acute lymphocytic leukemia
AML	Acute myeloid leukemia
AML	Acute myeloblastic leukemia
APB	ALT-associated PML body
AT	Ataxia telangiectasia
ATLD	Ataxia telangiectasia-like disorder
ATM	Ataxia telangiectasia mutated
ATM	Ataxia-Telangiectasia Mutated Kinase
ATMK	Ataxia telangiectasia mutated kinase
AuNP	Au nanoparticles
AZT	Azido-dideoxy-thymidine
BC	Breast cancer
B-CLL	B cell- chronic lymphoid leukemia
BCSCs	Breast cancer stem cell
BER	Base excision repair
BFB	Breakage-fusion-bridge
BLM	Blooms syndrome gene
53BP1	p53-binding protein 1
BT	Brain tumor
CBX	Chromobox Homolog
CD24	Cluster of differentiation 24
CD44	Cluster of differentiation 44
CFI	Cancer Family Indices

CIC	Cancer initiating cells
CKAP4	Cytoskeleton associated protein-4
CLL	Chronic lymphoid leukemia
CML	Chronic myeloid leukemia
Cox2	Cyclo oxygenase
CR	Calorie restriction
CRAMP	Cathelin-related antimicrobial peptide
CRC	Colo rectal cancer
CSCs	Cancer Stem Cells
CST	Cdc13, Stn1 in mammalian cells and Ten1
CUP	Cancer of unknown primary
CX	Telomerase reverse primer
DFS	Disease-free survival
DKC-1	Dyskerin-1
DNA	Deoxynucleic acid
DNAPKcs	DNA-dependent protein kinase catalytic subunit
DNMTs	DNA methytransferases
dNTPs	Deoxynucleotide triphosphates
DSB	Double-strand breaks
DSBR	Double strand DNA break repair
dTTP	Deoxy thymine tri phosphate
dUMP	Deoxy uridine mono phosphate
EAIF	Environmental Acquired Influential Factors
EC	Endometrial cancer
ECCR	Excision repair cross –complementing
ECTR	Extrachromosomal telomere repeat
EI	Environmental Index
ELIPA	Elimination of PCR assay
EMSA	Electrophoretic mobility shift assay
EMT	Epithelial and mesenchymal transitions
EPCs	Endothelial progenitor cells
ER	Estrogen receptor
ESCs	Embryonic stem cells
EST	Ever-shorter telomere
FA	Fanconi anemia
FDA	Food and drug administration
FF	Family factor
FF	Flow fish
FH	Family history
F-TRAP	Fluorescent- TRAP
G	Genomics
G	Guanine
GAPDH	Glyseraldehyde 3-phosphate dehydrogenase
GBM	Glioblastoma multiforme
GI	Gastrointestinal

GPI	Glycosyl-phosphatidylinositol anchor
GSCs	Glioma stem cells
H3K9	Histone 3 lysine 9
H3-K9	Histone 3 trimethylated at lysine 9
H4-K20	Histone 4 trimethylated at lysine 20
HA	Hyaluronic acid
HDACs	Histone deacetylase
HL	Hodgkin lymphoma
HMSCs	Human mesenchymal stem cells
HMTase	Histone-Methyltransferase
HnRNP A1	Heterogeneous nuclear ribonucleoprotein A1
HP1	Heterochromatin protein 1
HPA	Hybridization protection assay
HR	Homologous recombination
hRAP1	Human repressor activator protein 1
HSA	Heat stable antigen
HSCs	Hematopoietic stem cells
hTEP1	Human telomerase associated protein 1
hTERT	Human telomerase reverse transcriptase
hTR (hTER)	Human telomerase RNA
ICM	Inner cell mass
IDC	Invasive Ductal Carcinoma
IDH1	Isocitrate dehydrogenases 1
IF	Immunofluorescence
IGF-1	Insulin growth factor 1
IGFI	Insuline-like growth factor
IIGC	Instinct Influential Genetic Characteristics
IL-2	Interleukin 2
IL-6	Interleukin 6
INF-Gama	Interferon-Gamma
IP6	Inositol hexaphosphate
iPSC	Induced pluripotent stem cells
ISTRAP	In situ TRAP
KS	Kaposi's sarcoma
Ku	A protein's name
LFS	Li-Fraumeni's syndrome
LINE	Long interspersed nuclear element
LOH	Loss of heterozygosity
LTL	Leukocyte telomere length
M/A	Mitotic/apoptotic
MBP	Methyl binding protein
MDS	Meylodysplastic syndrome
MEN1	Multiple endocrine neoplasia type 1
MEN2	Multiple endocrine neoplasia type 2
MLP	Myosin-like protein

MMR	Mismatch repair
mMSCs	Murine mesenchymal stem cells
MRE11	Meiotic recombination 11
mRNA	Messenger Ribonucleic Acid
MRX complex	Mre11/Rad50/Nbs1
MSCs	Mesenchymal stem cells
MTHFR	Methylen tetra hydro folate reductase
NBS1 or NBN	Nijmegen breakage syndrome 1 or Nibrin
NER	Nucleotide excision repair
NF2	Neurofibromatosis type 2
NFl	Neurofibromatosis type1
NHEJ	Non-homologous end joining
NHL	Non-Hodgkin's lymphoma
NHSCs	Non-hematopoietic stem cells
OM	Other malignancies, excluding BC
OS	Overall survival
PAGE	Polyacrylamide gel electrophoresis
PARP	Poly(adenosine diphosphate-ribose) polymerase
PC	Prostate cancer
PCNA	Proliferating cell nuclear antigen
PCR	Polymerase chain reaction
PCR-FTD	Polymerase chain reaction free telomerase detection
PGM1	Phosphoglucomutase1
PIKK	Phosphoinositide 3-kinase related kinase
PIP1	Pot-1 interacting protein
PKC	Protein kinase C
PML	Promyelocytic leukaemia
PNA	Peptide nucleic acid
POT1	protection of telomeres 1
POT1	Protection of telomeres protein 1
PP2 A	Protein phosphatase 2 (PP2)
pRb	The Retinoblastoma protein
PTEN	Phosphatase tension human homology
PTEN	Phosphatase and tensin homolog
PTOP	POT1 and TIN2 organizing protein
PUFA	Polyunsaturated fatty acids
Q-FISH	Quantitative fluorescence in situ hybridization
RAP1	Repressor/activator protein 1
RAR-β	Retinoic acid receptor- β
Rb	Retinoblastoma
RB1	Retinoblastoma protein 1
RBL	Retinoblastoma-like
RCC	Renal cell carcinoma
RCCs in VHL	Renal cell carcinomas in von Hippel-Lindau
RNA	Ribonucleic Acid

RNAi	RNA interference
RNP	Ribonucleoprotein
ROS	Reactive oxygen species
RQ	Real-time quantitative assay
RTBP1	Rice telomere binding protein 1
RT-PCR	Real time-polymerase chain reaction
S	Somatic
SAH	S adenosine hydrolysis
SAM	S adenosine methionine
SCID	Severe combined immunodeficiency
SFA	Saturated fatty acid
SHH	Sonic hodgehog
Shp-2	SH2-containing protein tyrosine phosphatase
SIRs	Standardized Incidence Ratios
SNP	Single-nucleotide polymorphism
SNPs	Single nucleotide polymorphisms
SPA	Scintillation proximity assay
SPB	Spindle pole body
ss	Single strand
STELA	Single Telomere Length Analysis
SUV39 H	Suppressor of variegation 3–9 homologue
T	Thymine
TA	Telomerase activity
TANK	TRF1 interacting ankyrin-related ADP-ribose polymerase or Tankyrase
TAP-1	Telomerase associated protein-1
TBA	Target Based Aging
TCAB-1	Telomerase Cajal body protein −1
TCAB1	Telomerase and Cajal body protein1
TCC-UUT	Transitional cell carcinoma of the upper urinary tract
TDMs	Telomeric DNA-containing double-minute chromosomes
TER	Telomerase RNA comoponent
TERBF1	Telomerase repeat binding factor −1
TERC	Telomeric RNA component
TERC	Telomerase RNA component
TERT	Telomerase reverse transcriptase
TGF-beta	Transforming growth factor –*beta*
TGF-β	Tissue growth factor-β
TIN2	TRF1-interacting nuclear factor 2
TL	Telomere length
TLM	Telomere length maintenance
TMA	Transcription-mediated amplification
TPE	Telomere position effect
T-PLL	T-promeyelocytic leukemia
T-PLL	T-Promtelocytic leukemia

TPP1	Tripeptidyl-peptidase 1
TR	Template RNA
TR	Telomere regulation
TRAF-1	Telomeric repeat binding factor-1
TRAP	Telomerase repeat amplification protocol
TRD	Telomere rapid deletion
TRE	Elongation of telomeric repeats
TRF	Terminal Restriction Fragment Length
TRF-1	Telomere repeats factor-1
TRF1 or TERF1	Telomere repeat binding factors 1
TRF-2	Telomere repeats factor-2
TRF2 or TERF2	Telomere repeat binding factors 2
TRF2	Telomere restriction fragment 2
TRFA	Telomere restriction fragment analysis
Trim	Trimethylation
tRNA	Transfer ribonucleic acid
TS	Telomerase substrate primer
TSG	Tumor suppressor gene
UV	Ultraviolet
WRN	Werner syndrome gene
WS	Werner syndrome

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